REMARKS

The Office Action mailed January 13, 2003, has been received and carefully reviewed. Reconsideration and withdrawal of the rejections of the claims of the above-identified application is respectfully requested. Claim 153 has been rewritten as new claim 211 and incorporates the limitations of claims 151 and 152. New claims 212-214 are fully supported by the specification and figures as originally filed, for example at page 30, line 26 through page 31, line 7 and FIG. 5 for claim 212, page 27, lines 23-26, page 28, lines 13-20 and page 32, lines 22-30 for claim 213, and page 13, lines 3-5 for claim 214. Claim 198 has been amended to clearly define a kit. No new matter has been added.

Information Disclosure Statement

The English equivalent of EP 0 186 799 is US 4,861,711, submitted herewith. Applicants request consideration of this reference.

Rejections Under 35 U.S.C. §103(a)

Claims 151, 154, 156 and 158-167 are rejected as unpatentable over Bergman (US 5,501,955) in view of May et al. (US 5,622,871). Claims 152, 153, 155, 157 and 168-181 are rejected as unpatentable over Bergman in view of May et al. as applied to claims 151, 154, 156 and 158-167, and further in view of Janeway et al. (Immunobiology 3rd ed.). Because the limitations of claims 152 and 153 have been incorporated into claim 151, the above rejections are addressed together.

With regard to new claim 211, corresponding with now canceled claims 151-153, there is no teaching in Bergman as to the use of first and second immobilized antibodies that would respectively bind to distinct binding sites or autoantigenic epitopes on a common antigen to provide detection of first and second autoantibodies. Furthermore, such a modification of the specific teaching of Bergman would not in any way have been contemplated by Bergman, or suggested by the teachings of Bergman, May or Janeway to a skilled artisan for the following reasons.

The use of first and second immobilized antibodies allows the possible detection of first and second distinct autoantibodies, respectively, recognizing distinct autoantigenic epitopes on a common antigen. Such detection of distinct autoantibodies for distinct autoantigenic epitopes would be unlikely to be possible with the test tube incubation conditions taught by Bergman. However, the use of a test strip as provided by the present invention with first and second antibodies immobilized at discrete positions on the test strip allows the detection of such distinct autoantibodies. This provides the advantage over and above the teaching of Bergman of allowing the detection of first and second distinct autoantibodies.

The Examiner has further cited Janeway as teaching multivalent antigens and antibody binding. Janeway is essentially a general background reference in the field of immunology, and would merely have provided a skilled artisan with a reference to the general principles known in immunology and which would have been well known to the skilled artisan. In this respect, while Janeway does indeed teach that antigens can be multivalent, this would have been well known to one of skill in the art. Janeway does not provide any guidance for one to modify the teaching of Bergman and May to include first and second immobilized antibodies in test strip format for detection of first and second autoantibodies.

Additionally, there is no expectation of success in adding a second immobilized antibody to a second, distinct, binding site on the antigen of Bergman or May. The mere knowledge, provided by Janeway, that some antigens have multiple distinct epitopes, does not provide the guidance or expectation of success for one to modify the assays of Bergman and May to include an additional immobilized antibody that binds a second distinct epitope on the antigen. Neither Bergman nor May teach or suggest the existence of two different autoantibodies binding two distinct epitopes on the antigens they are investigating. The entire disclosures of Bergman and May are directed to detecting the interaction of single antibody-antigen complexes. Thus, even with the general knowledge provided by Janeway, that some antigens have multiple epitopes, one of skill in the art would not be motivated to further modify the methods of Bergman or May to

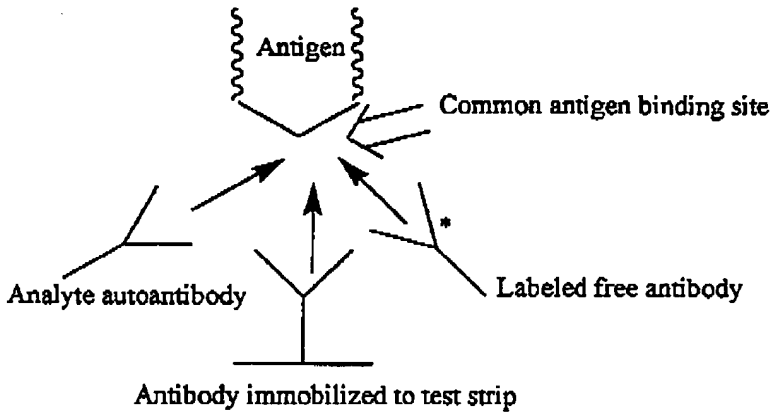
achieve the claimed methods and kits. The only motivation or suggestion of adding a second immobilized antibody to the method of Bergman is found in the instant specification. Absent this improper hindsight reconstruction, none of the cited references provide one of ordinary skill in the art with the motivation or expectation of success in modifying the method of Bergman to achieve the instant methods. Withdrawal of the rejection is respectfully requested.

The method of claim 168 provides a sensitive assay for use at the point of patient care, in which the presence of either first analyte, second analyte or both analytes is determined. This embodiment involves the simultaneous competitive binding of antibodies and autoantibodies to two distinct binding sites on the antigen. Bergman teaches an embodiment where autoantibody competitively inhibits binding of both an immobilized antibody and a free labeled antibody to the antigen, as illustrated by Figure 3. Figure 3 shows binding of both the immobilized and free labeled antibody to a common binding site on the antigen, as is described at column 7, lines 12 to 17.

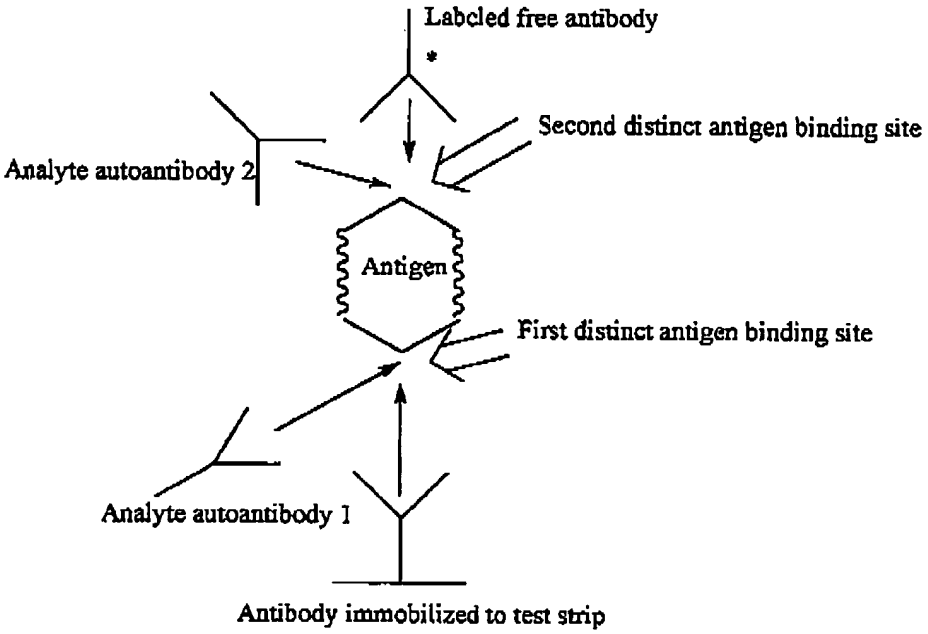
Although Figures 1 and 2 (see also the claims) illustrate the presence of distinct binding sites on the antigen as disclosed in Bergman, this is in the context of detecting autoantibody by competitive inhibition of binding to a single binding site on the antigen. Bergman does not teach or suggest autoantibody detection by synchronous competitive inhibition of antibody binding at more than one binding site of the antigen. In particular, Bergman does not teach or suggest a method wherein first and second autoantibodies respectively competitively inhibit binding of an immobilized antibody and a free labeled antibody to distinct binding sites on the antigen. The instant method of claim 168 employs an immobilized first antibody and a free labeled second antibody, where the immobilized and free (non-immobilized) antibodies bind distinct first and second binding sites on the antigen (not a common binding site) and this binding with the distinct binding sites is competitively inhibited by first and second autoantibodies. See the enclosed illustration of claim 168.

If a test strip assay was provided by modifying the above teaching of Bergman into test strip format, with both the immobilized antibody and the labeled non-immobilized antibody binding a common binding site of the antigen as required by the

teaching of Bergman, then it is unlikely the test strip assay would allow for the detection of autoantibodies. In such an assay, the labeled free antibody, immobilized antibody and analyte autoantibody would compete for binding to a common binding site on the antigen and this would not allow for a competitive assay where binding of the labeled antibody to the test strip (via the antigen – immobilized antibody) could provide a meaningful correlation as to the presence of autoantibody or autoantibodies in a test sample. Such competitive binding as envisaged by Bergman and if modified for use in a test strip as suggested by the Examiner would be as follows:



The instant invention on the other hand does allow for a meaningful correlation as to the presence of autoantibodies in a test sample as illustrated by the following:



In the present invention as discussed above, this is by virtue of the provision of an immobilized first antibody and a labeled non-immobilized second antibody binding to distinct binding sites on the antigen, allowing for a rapid and sensitive detection of autoantibodies to be carried out. This clearly provides advantages over and above the teaching of Bergman. Neither May nor Janeway teach or suggest the simultaneous competitive binding of antibodies and autoantibodies to two distinct binding sites on the antigen. Withdrawal of the rejection is respectfully requested.

New claim 213 specifies a test strip including a sample application zone comprising means for separating blood cells from plasma of a blood sample being screened. The inventors have found that the use of such separating means on the test strip of their invention allows the provision of a rapid autoantibody test that can be used at the point of patient care for patient blood samples to be screened. The use of such blood separating means was in no way envisaged or taught by the cited prior art for the

reasons explained above and as such cannot be viewed as a routine modification of the teaching thereof, and provides significant advantages for use in screening blood samples at the point of patient care. This embodiment of the present invention is clearly described with reference to the use of kits as shown in the Figures of the present application.

In Bergman, for the sample to be investigated Bergman neither describes nor suggests the use of such a separation step. Indeed such a separation step would be unnecessary for use in the test tube incubation conditions taught by Bergman. May similarly does not teach such a separation step and one of ordinary skill in the art would not consider modifying May to include such a separation step because May is essentially concerned with the testing of urine samples.

Claim 213 specifies a substrate including a sample application zone comprising means for separating blood cells from plasma of a blood sample being screened. The inventors have found that the use of such separating means on the test strip of their invention allows the provision of a rapid autoantibody test that can be used at the point of patient care for patient blood samples to be screened. The use of such filter means was in no way envisaged or taught by the cited prior art for the reasons explained above and as such cannot be viewed as a routine modification of the teaching thereof, and provides significant advantages for use in screening blood samples at the point of patient care.

New claim 214 specifies the use of immobilized antibody on the test strip, together with the use of labeled antigen, with competition for antigen binding occurring between the immobilized antibody and autoantibody for a common binding site of the antigen. While Bergman teaches the use of an immobilized antibody and an antigen, with analyte autoantibody competing with binding of the immobilized antibody to a common binding site of the antigen, the teaching of Bergman is limited to the use of free antibody as the labeling means. In particular, the use of labeled antigen would be contrary to the teaching of Bergman and the requirement therein that "crude" or "non-purified" antigen should be employed. In this respect, Bergman clearly teaches against the use of labeled antigen, see column 3. One of ordinary skill in the art would not have been motivated to modify the teaching of Bergman into test strip format as taught by May, with the use of

labeled antigen because Bergman specifically teaches methods for avoiding the use of labeled antigen.

Claims 182-197 are rejected as unpatentable over Bergman in view of May et al. as applied to claims 151, 154, 156 and 158-167, and further in view of Foster et al. (US 4,444,879). Foster is cited for teaching a kit in which an immunoassay of the invention is incorporated. The combination of Bergman and May fails to teach or suggest the basic elements of the claims for the reasons provided above. Foster does not teach or suggest what Bergman and May lack. Therefore, the combination of Bergman, May and Foster also fails to teach or suggest the claimed invention.

Claims 198-210 are rejected as unpatentable over Bergman in view of May et al. and Janeway as applied to claims 151-181, and further in view of Foster. The combination of Bergman, May and Janeway fails to teach or suggest the basic elements of the claims for the reasons provided above. Foster does not teach or suggest what Bergman, May and Janeway lack. Therefore, the combination of Bergman, May, Janeway and Foster also fails to teach or suggest the claimed invention.

It is respectfully submitted that each of the presently pending claims is in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicants' representative at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted,

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